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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,278	03/15/2005	Hiroshi Sato	3190-074	4130

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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,278	SATO ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7-9,11,12,14-16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,13,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/9/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/05; 5/05; 12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 30, 2006. Currently, claims 1-19 are pending. Claims 7-9, 11-12, 14-16, 18 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I, Claims 1-6, 10, 13, 17, 19 in the paper filed November 30, 2006 is acknowledged.

The response asserts that the corresponding International application has found unity of invention and that the unity of invention should apply in the instant application. This argument has been reviewed but is not persuasive because the two groups lack a special technical feature. The prior art, namely Huang (Pharmacokinetics, Vol. 10, pages 539-544, 2000) specifically teaches the polymorphism in the UGT gene, exon 5, nucleotides 1456 and amino acid position 486. Thus, this polymorphism is not a contribution over the prior art.

Unity of invention considerations do not require burden on the part of the examiner. However, even if burden was required to be established in an international stage application, search of the nucleic acids and search of the methods are not coextensive. A search of the nucleic acid does not require a search of drug metabolizing activity required by group I.

Claims 7-9, 11-12, 14-16, 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 7-9, 11-12, 14-16, 18 are drawn to an invention nonelected with traverse in the paper filed November 30, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application is a 371 of PCT/JP03/01475, filed February 13, 2003 and foreign priority application 2002-235029, filed August 12, 2002.

It is noted that a translation of the foreign document has not been received.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 5-6, 13, 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a mutation in exon 5 of a gene coding for UGT.

The specification teaches uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases, UGT) are enzymes that catalyze glucuronidation of various drugs (page 1). The specification teaches that the different UGT enzymes conjugate different substrates (page 1-2). The specification analyzes 2-amino-5-nitro-4-trifluoromethylphenol glucuronide which is glucuronidated by UGT. The specification states that "as long as drugs to be assayed by the invention are glucuronidated by UGT, they are useful for assay of their metabolism" (page 15, lines 20-26). The specification provides a short list of examples (page 15-16). The specification measured UGT

activity with 2-amino-5-nitro-4-trifluoromethylphenol glucuronide as a substrate (page 20).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With respect to claims which encompass variants, as provided in Example 11 of the Written Description Guidelines, no common structural attributes identify the members of the genus. The current claims encompass a large genus of nucleic acids which comprise variants in exon 5; exon 1-4 of the UGT gene. The genus includes an enormous number of variants, polymorphisms and mutations for which no written

description is provided in the specification. This large genus is represented in the specification by only the particularly named polymorphism in exon 5 for which data is provided, namely 1456 TAC-GAC, also designated Tyr486Asp. Given the broad language of mutations recited in the claim, this genus encompasses SNPs, deletions, insertions, translocations, microsatellites, for example.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, variants of the UGT gene alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of a UGT gene relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms. The polymorphisms shown are not representative of the genus of any polymorphism associated with drug metabolizing activity of UGT because it is not clear which polymorphisms in the UGT nucleic acid would have the same effect. One of skill in the art would conclude that applicant was not in possession

of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims .1-6, 10, 13, 17, 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to an assay method for drug metabolizing activity of UGT comprising a step of detecting a mutation in exon 5 region of a gene coding for UGT.

The claims broadly encompass any mutation, any drug metabolizing activity in any organism.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to

overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification teaches uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases, UGT) are enzymes that catalyze glucuronidation of various drugs (page 1). The specification teaches that the different UGT enzymes conjugate different substrates (page 1-2). The specification analyzes 2-amino-5-nitro-4-trifluoromethylphenol glucuronide which is glucuronidated by UGT. The specification states that "as long as drugs to be assayed by the invention are glucuronidated by UGT, they are useful for assay of their metabolism" (page 15, lines 20-26). The specification provides a short list of examples (page 15-16). The specification measured UGT activity with 2-amino-5-nitro-4-trifluoromethylphenol glucuronide as a substrate (page 20). The UGT gene mutation Y485D (homozygous) was 8% UGT relative activity (page

20). The UGT gene mutation Y485D (heterozygous) was 36%. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims are drawn to any exon 5 mutation. The specification teaches a single mutation in exon 5 of the UGT gene. The skilled artisan would be required to perform further unpredictable and undue experimentation to practice the broad scope of the claimed invention. The skilled artisan would be required to anazlye the UGT gene for additional mutation in exon 5 and then further perform trial and error experimentation to determine the effect of the polymorphism on drug metabolism. While one could conduct such experimentation to determine whether SNPs or mutations are associated with a particular drug metabolizing activity, as described by the art above, the results of such experiments are unpredictable and undue. The art clearly teaches different mutations in the same disease are not associated with the same disease indicating the variability of mutations and their affects. Thus, for the skilled artisan to practice the broad scope of the claims, analysis of additional mutations and drug metabolism would be required.

The claims are drawn to any drug metabolizing activity. The specification teaches that uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases, UGT) are enzymes that catalyze glucuronidation of various drugs (page 1). The specification teaches that the different UGT enzymes conjugate different substrates (page 1-2). The specification analyzes a single drug, namely 2-amino-5-nitro-4-trifluoromethylphenol glucuronide which is glucuronidated by UGT. However this single drug is not representative of the class of drugs glucuronidated by

UGT. The skilled artisan would be required to perform additional experimentation on the other members of the class of drugs that are affected by UGT to determine whether the polymorphisms in UGT, including the exon 5 mutation at 1456 of the instant specification, are associated with drug metabolizing activity.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art of associating polymorphisms with particular condition, the broad scope of the claims would not be enabled at the time the invention was made. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized.
Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-6, 10, 17, 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-6, 10, 17, 19 are indefinite because it is unclear whether the method is drawn to an assay for drug metabolizing activity of UGT or a method for detecting a mutation in exon 5 region of a gene coding for UGT. The preamble is directed to an assay method for drug metabolizing activity of UGT but the final process in the method is for detecting mutations. Thus, it is unclear whether the claims are drawn to a method for drug metabolizing activity or a method of detecting mutations in exon 5 of UGT.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-6, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al. (Pharmacogenetics, Vol. 10, pages 539-544, 2000).

Given the rejection under 112/2nd above where it is unclear whether the method is for drug metabolizing activity of UGT or a method for detecting mutations in an exon 5 region of a gene coding for UGT, the following rejection is applied.

Huang et al teaches variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwanese individuals. Huang teaches activity of UGT1 may influence the concentration of serum bilirubin. Huang teaches a variation site in UGT1A1 gene in exon 5, at nucleotides 1456 which is a TAC to GAC substitution which corresponds to the amino acid substitution Tyr486Asp (page 541, Table 2)(limitations of Claims 3-4, 17). Huang teaches analyzing the serum bilirubin levels for the variants. Huang further teaches analysis of the promoter region of UGT1, and position 686 (Table 2)(limitations of Claim 2, 5-6).

9. Claims 1, 3, 4, 13, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Ito et al. (Eur. J. Clin. Pharmacol. Vol. 58, pages 11-14, February 16, 2002).

Ito teaches an effect of a conserved mutation in uridine diphosphate glucuronosyltransferase 1A1 and 1A6 on glucuronidation of a metabolite of flutamide. Ito examines the Y486D mutation in UGT1A1 for 2-amino-5-nitro-4-trifluoromethylphenol, which is a major metabolite of flutamide, a nonsteroidal antiandrogenic agent (abstract). Ito concludes that patients with Y486D may accumulate excessive 2-amino-5-nitro-4-trifluoromethylphenol, which might lead to

unexpected toxicity (abstract). The mutation corresponding to Y486D of UGT1A1 is conserved in all UGT1 isoforms (page 13, col. 1).

10. Claims 1, 3, 4, 13, and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Gagne et al. (Molecular Pharmacology, Vol. 62, No. 3, pages 608-617, August 16, 2002).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Gagne teaches common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Gagne teaches analysis of Y486D which demonstrated an 11% residual activity. Gagne teaches that clinical trails have established irinotecan in combination with 5-fluorouracil/leucovorin as the new standard of care in the first-line treatment of metastasized colorectal cancer (page 608, col. 1). Gagne teaches analyzing the functional effect of known common allelic variations of UGT1A isoenzymes involved in SN-38G formation including Y486D (UGT1A1*7). Gagne teaches that as expected an important decrease in SN-38-G formation was observed for the UGT1A1*7 variant (page 616, col. 1).

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J Goldberg

Jeanine Goldberg
Primary Examiner
February 5, 2007